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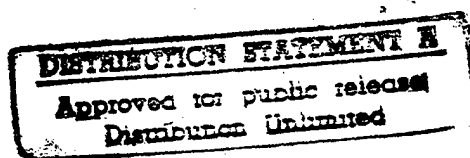
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PATHOLOGICAL ANATOMY OF AFFECTIONS CAUSED BY TOXIC SUBSTANCES

- USSR -

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PATHOLOGICAL ANATOMY OF AFFECTIONS CAUSED BY TOXIC SUBSTANCES

[The following are translations of three articles written by S. S. Vayl' in the book entitled above, Leningrad, 1958, pages 3-32.]

From the Author

Under war conditions toxic substances (TS) can be used as a means of mass destructions of military contingents and civilian population. To prevent the harmful effect of TS on the human organism and to eradicate most effectively the sequels of poisoning, every physician must have a clear conception of the origin, pathology, clinical symptoms, and therapy of affections caused by TS. To diagnose and treat TS affections, one must be familiar with their pathological anatomy and pathogenesis.

The State Publishing House of Medical Literature placed before me the task of writing a brief monograph which would include the facts known at present on pathological anatomy of TS affections -- a short manual intended not for toxicologists but for practicing physicians who need to render diagnosis and treatment to poisoned individuals.

It is obvious that a book, even of a small size, must reflect the present-day level of knowledge of the anatomy and pathogenesis of affections caused by TS action. In recent years there has been a change in a number of concepts on the mechanism of TS effect on the organism, new studies appeared which widen the range of knowledge on the character of these changes. These data, naturally, had to be included in the present manual.

The reader will find in this book an exposition of the pathological anatomy of affections caused by TS known as far back as the period of the imperialistic war of 1914-1918. These data are of interest even at the present time, first of all, because of "old" TS (for instance, mustard gas) are not put away in archives, and because a familiarization with their toxicology is even now essential. Secondly, in the case of such TS as diphosgene, mustard gas, lewisite, prussic acid, and hydrogen arsenide, one can familiarize oneself with the basic mechanisms of the action and character of affections caused by TS in the organism. It is difficult to predict precisely which new TS might be suggested in the future for mass destruction of people, but a physician well versed in the pathogenesis, anatomy, and clinical picture of affections caused by the basic representatives of well-known TS will be equipped for the quick

diagnosis of the effects of unknown TS and for the organization of necessary preventive and therapeutic measures.

In recent years new TS were synthesized which, because of several characteristics (high toxicity, rapid effect on the organism in various forms of application) attracted the attention of specialists and must be made known to practicing physicians. Therefore, I faced the task of including in this book information of the pathological anatomy of such TS.

Special attention was devoted to the so-called phosphoro-organic substances (PhOS) and trichlortriethylamine (nitrogen mustard gas). I attempted to clarify these sections as thoroughly as possible.

In following the traditions of the clinico-anatomical trend of our native pathological anatomy, I tried to carry out the description of pathologo-anatomical data in such a way that they would easily be juxtaposed with the clinical manifestations of the toxic effects. In all cases attention was concentrated on the pathogenesis and dynamics of the development of affections, on their complications, outcome, and the remote sequels of poisoning.

It is important from practical considerations to learn to recognize TS according to the character of affections produced. With this in view, a special chapter (VI) is devoted to differential pathologoanatomical diagnostics; it includes a number of tables which aid in mastering the data and facilitate the knowledge of the character of TS on the basis of changes detected in the organism macro- and microscopically. Special attention is devoted in this chapter to the differential diagnosis of affections caused by PhOS and nitrogen mustard gas.

In a book, the basic content of which is the description of morphological changes, the illustrative material is very important. I made an effort to improve the clarity of the text with corresponding photos, illustrations, and microphotographs which would reveal all basic affections caused by various applications of TS.

I trust that, despite its small size, the various medical specialists will find in this manual basic information on the pathological anatomy and pathogenesis of affections caused by TS which will prove useful in interpreting the clinical picture of corresponding poisonings.

Chapter 1

General Data on the Effect of TS upon the Organism

Toxic substances which can be employed as a means of mass affection of people differ in their chemical composition. The peculiarities of their chemical structure largely determine the character of their action on the organism; however, the forms of reaction of the organism to the irritant may exert a substantial

influence on the pathology, clinical pictures and outcome of poisoning. Thus, certain TS, dissimilar in their chemical composition, may produce affections fairly similar in their manifestations. For example, there is quite a resemblance between affections caused by mustard gas and by lewisite, and between changes caused by prussic acid and by PhOS. On the other hand, the same TS is of different toxicity to various animals, and in a given animal at different times dissimilar afflictions; thus, for example, mustard gas fumes which cause in humans and certain animals pronounced affections of the tracheal mucosa, as a rule influence this organ only slightly in guinea pigs.

The effect of TS on the human organism is often judged on the basis of an experimental study. For a sound judgment, the action of TS must be observed on animals of different species; and one must take into account that the affections of certain organs of one animal may resemble the changes of analogous human organs induced by the same TS, and that a different animal is needed to produce a model of affections of other organs. Thus, for instance, pneumonia caused by mustard gas in a cat resembles markedly the pulmonary inflammation in humans from the same TS; but, if we wish to produce a model of mustard gas dermatitis, the experiments will have to be conducted not on cats or dogs but on the skin of a suckling pig.

TS may affect the organism in various ways. Some TS (of the so-called stable ones, such as mustard gas and lewisite) may contaminate objects with which people come into contact -- soil, arms, cloth, etc., food and water. If a TS from the soil or from various objects, or directly comes into contact with the skin, the latter is contaminated, and a general poisoning can occur through the integumenta (the so-called skin application of TS). The entry of contaminated food products (food application of TS) into the organism leads to the initial affection of the organs of digestion frequently accompanied by grave general poisoning. Fumes of the same substances cause poisoning which manifest itself in pronounced phenomena of affection of the respiratory tract and lungs; in certain TS (for instance, so-called suffocating TS, hydrogen arsenide) the respiratory application represents the means of their effect on the organism.

Certain TS (mustard gas, lewisite), upon direct contact with the tissue of the organism, produce, even in very small doses, inflammatory and destructive affections (the so-called local effect of TS); large doses of the same TS, parallel with pronounced local changes, cause phenomena of general poisoning of varying intensity. Other TS (prussic acid and the so-called phosphines) upon contact with the skin and mucous membranes, do not affect them but, by absorption, may rapidly produce such widespread effect on the organism that the result is fatal.

General and local changes which originate in various ways in the organism are interconnected and represent one entity. Local inflammatory, dystrophic, and necrotic changes in the skin, respiratory tract, lungs and the digestive tract cause a number of reactive changes in the entire organism -- particularly in the nervous system, hemopoietic and digestive organs, and a number of parenchymatous organs. On the other hand, the so-called general poisoning impair the nerve and blood supply of various organs and is accompanied by circulatory and dystrophic changes.

The mechanism of the local as well as general effect of TS on the organism are diverse, complex, and nonuniform for various TS. Upon contact with the organism, TS act first on circulatory and tissue receptors; at the same time, the blood and lymph circulation are impaired. Oedema, hyperemia, hemorrhages and inflammation and dystrophic changes often terminate in necrosis.

The general effect of TS on the organism is connected with the absorption of the toxic substance in the blood and the circulation (or the products of its disintegration or transformation) which affects the tissues which it reaches; it is designated by the term resorbtive action. In contacting the tissues, the poison penetrates the blood, is carried through the entire organism is distributed among various organs (often unequally), undergoes changes in the tissues, and is eliminated in varying degrees. In being distributed through the organism and affecting it as a whole, or affecting separate organs or tissues, the toxic substance produces a number of changes of the structure and functions which may not be uniform at various stages of the TS action. At the same time, while causing irritation of the receptor devices, the TS may be reflex action impair the innervation and vascularization of tissues, which also lead to pronounced structural and functional disturbances.

The neurogenic, particularly the reflex, mechanism may cause the emergence of the so-called local changes due to TS. It is well known, for instance, that inhalation of diphosgene fumes causes pulmonary edema (serous pneumonia) accompanied by a number of general changes. Nothing of the kind will happen if the animal is poisoned during complete narcosis. If a cat, under complete narcosis, is subjected to the effect of several (five and more) lethal doses of diphosgene, no changes in the lungs of the animal and in its entire organism will take place; pulmonary edema has a reflectory pathogenesis; if the possibility of a reflectory mechanism is eliminated through narcosis, neither local inflammatory pulmonary changes, or general systemic changes (particularly, affections of the central nervous system) can take place. It is interesting that in cases where no general narcosis is experimentally induced, and only the cerebral cortical activity is impaired (through the use of so-called "large doses" of bromine), diphosgene causes edema of the lungs, but the course of the pathological

process is distorted and pneumonia assumes a protracted character, and becomes chronic.

In some cases the affections caused by TS in the areas of their contact with the tissues are so serious that they themselves may cause a grave disease and death; such are, for example, pneumonia and gastritis caused by the action of mustard gas and lewisite. Of course, in these cases a general systemic poisoning occurs, but it is not very easy to evaluate its significance and specific role. Much more definitely pronounced are the manifestations of general poisoning when at the time of TS application affections appear which cannot account for the grave general state of the organism; this happens, for example, in cases of application of large doses of mustard gas (or lewisite) to a small surface of the skin. Under such conditions of poisoning, the changes which cause the gravity of the disease and are manifested mainly in the affections of the nervous system, can be demonstrated most convincingly. The general effect of TS on the organism influences the course of local changes (Particularly, in retarding reparative processes and inhibiting regeneration) and contribute to the transition of acute inflammatory changes into chronic ones.

Of special importance in the pathology of toxic effects are the affections of the nervous system. Certain so-called general TS act mainly on the nervous system, especially the central one; PhOS TS may serve as an example. Changes in the cerebrum, vegetative neural nodes, and peripheral neural apparatus play a substantial role also in the poisoning by many TS not related to general toxic substances. It is necessary to note that the general effect of a number of TS depends to a considerable degree also on blood changes and on the affection of the hemopoietic system. Thus, in carbon monoxide poisoning a transformation of hemoglobin into carboxyhemoglobin takes place; hydrogen arsenide possesses a markedly pronounced hemolytic action; mustard gas and lewisite inhibit hemopoiesis and cause destructive affections of the myolepoietic elements.

Environmental conditions affecting the organism unfavorable aggravate the course of affections induced by TS. Thus, for example, mustard gas causes a more gravely proceeding poisoning accompanied by more pronounced changes in some organs when the organism is chilled, overheated, or fatigued.

The destructive changes caused by TS, especially because they occur when the nerve and blood supply are impaired, create the soil for tissue infection which obtains particularly favorable developmental conditions from the trophic impairments. Thus the course of the toxic process is complicated.

Diseases caused by certain TS proceed at highly accelerated pace and may quickly terminate in death. Especially violent and of lightning speed are the toxic effects of certain general toxic

substances (prussic acid, phosphoorganic TS). The rapidity of the development of the disease depends on the dose as well as on the character of the TS action on the organism; for instance, in a cutaneous application of lethal doses of mustard gas and lewisite, the rate of development of pathological changes from the mustard gas will be slower and death occurs later than from lewisite. With smaller doses of TS, the disease may assume a protracted character, in some instances ending fatally at a later time; in others, leading to disability. The remote sequels of toxic effects have been investigated for many TS (diphosgene, chlorine, mustard gas, lewisite, carbon monoxide, etc.).

One speaks of a lightning death if the victim's life lasts between a few minutes and one to two hours. If death occurs within the first three days after poisoning, the episode is called acute (death in the acute stage); if life lasts from four to ten days, one speaks of a subacute period, and after ten days -- of a remote period of poisoning. The latter type may extend for many months, and of course the sequels of poisoning two weeks later or a year later may differ substantially from one another; therefore, when one speaks of affections of a remote period, the duration should be indicated.

The affections of the entire organism, individual organs, and tissue caused by TS vary considerably in their gravity and outcome. These depend on the TS properties, the type of application, dose, specific and individual sensitivity of the organism, conditions under which it existed before and after poisoning, the time and nature of first aid, and the character and effectiveness of therapy. A disease caused by TS may end in recovery, leave morphological changes and functional disturbances, cause various degrees of disability, or lead to death. In laboratory tests of TS toxicity one speaks of a conditional lethal dose if not less than 50 percent of the poisoned animals die, of a minimum lethal dose if the deaths equal 75 percent, and an absolute dose if all poisoned animals perish.

Morphological investigation plays a prominent role in the study of the pathology of poisonings; at the same time, such study involves considerable difficulties. The pathologo-anatomist must, first of all, establish the presence of changes caused by TS; when death has approached rapidly they may be very scarce, especially on post mortem examination. Slight hemorrhages and dystrophic changes in the parenchymatous organs, affections of neural cells and fibers, and the pathology of the hemopoietic system require thorough histological and cytological study. The task of the pathologist is facilitated if the method of TS application and the duration of the patient's life after poisoning are known.

The morphological findings are particularly scarce in cases of lightning death, or during the first few hours after the TS action, because under such conditions many changes do not develop

to the extent of permitting morphological study. Many difficulties arise also in cases of death during the remote period; the changes characteristic to TS are already absent at this time and are substituted by less specific changes which can not be justifiably attributed to the TS.

Affections caused by TS, in themselves, are as a rule of little specificity; the characteristic pathological picture is not always present. Nevertheless, an experienced pathologist-toxicologist utilizing the aggregate of even small pathologoanatomical findings and skillfully comparing them may be able to establish the presence of poisoning and determine its cause.

In the post-mortem examination the pathologist must not only detect all affections caused by TS but also use his findings for a differential diagnosis. This task is particularly urgent under wartime conditions, because the pathologoanatomical examination is an important means of ascertaining the character of TS action and its relation to certain known groups of TS, thus aiding the clinician in outlining the treatment of those who were poisoned with the same TS but who remained alive. Such differential diagnosis requires good knowledge of the pathological anatomy of all TS which might be employed under wartime conditions. I shall return to a more detailed analysis of this question at the end of the book (Chapter IV).

To make clinical use of the data of the pathologoanatomical autopsy and histological examination, dynamics of the morphological changes must be studied and compared with clinical symptomatology and investigations and data. In studying the development of affections the general changes which serve as the background of the development of local affections, and especially the role of the impairment of innervation and vascularization of tissues, the pathologoanatomist enters into the work on clarification of the pathogenesis of affections caused by TS, and supplies the clinic with valuable data in this respect.

The mechanisms of action of various TS on the organism is complex, and their pathogenesis, morphology, and clinical picture is of such little specificity despite their diversity that we still do not possess a satisfactory clinicoanatomical classification of TS. To familiarize the clinician with the most important TS and to make clinicoanatomical comparisons, the TS can be divided into the following groups:

- 1) TS with most pronounced general toxic effect (phospho-organic TS, prussic acid, hydrogen arsenide, and carbon monoxide);
- 2) The so-called suffocating TS (phosgene, diphosgene, chlorine, and phosgene chloride);
- 3) Mustard gas and trichlorethylamine;
- 4) Lewisite;
- 5) TS with the most pronounced irritating effect on the

mucous membranes of the upper respiratory tract and eyes (adamsite, diphenylchlorarsine, etc.). Since these TS do not cause permanent morphological changes in their usual concentrations, they will not be analyzed in this book.

The description of the pathologic-anatomical picture of affections caused by TS of the first four groups will be presented, together with an account of their various applications and the duration of life of poisoned individuals. This will enable us to give the pathologic-anatomical characteristic of each of the described TS, which the clinician will be able to compare with the pictures of poisoning observed at a patient's bedside.

Chapter II

The So-Called General Toxic Substances

Elimination of certain TS under the indicated name has, as had already been mentioned, a conditional character since the majority of TS possess a pronounced general toxic effect. The reason for singling out such TS as PhOS, prussic acid, hydrogen arsenide, and carbon monoxide is the fact that these substances exert a particularly strong effect on the nervous system (the central nervous system primarily) and blood without causing any appreciable effects in the areas of the initial contact with tissues (organs of respiration, digestion, and skin). These TS differ from each other in the mechanism of action of the organism and the toxic picture which they produce (certain common characteristics can be noted in the action of prussic acid and phosphoroorganic TS); therefore, each of these substances requires a special analysis and a clarification of the characteristic affections and their pathogenesis.

Phosphoroorganic Toxic Substances

Phosphoroorganic toxic substances (PhOS) may have substantial significance as a means of affection of people as the result of a combination of properties: high toxicity, ability to cause poisoning upon contact with the skin, respiratory, and the digestive tracts, rapid onset of grave symptoms of poisoning connected with the affection of various sections of the nervous system (especially the central one), and marked lethality in any form of application.

The representatives of this TS group are:

- a) "Tabun" -- ethyl ether of dimethylamide of cyanophosphoric acid; a colorless liquid with a slight odor of bitter almond;
- b) "Zarin" -- isopropyl ether of acid fluoride of methylphosphinic acid; colorless liquid, odorless;

c) "Zoman" -- pinacolyl ether of acid fluoride of methylphosphinic acid; colorless acid; colorless liquid, odor of camphor.

Toward humans the PhOS possess high toxicity; of laboratory animals the most sensitive to PhOS are cats and rabbits; less susceptible are guinea pigs and rats..

Various representatives of the PhOS cause toxic effects analogous to the pathological anatomy and clinical picture of poisoning, and these will therefore be described in one section.



Fig. 1.

PhOS. A -- pronounced myosis (eye of a rabbit);
B -- marked myosis (eye of a cat).

The general toxic effect of PhOS is manifested via every means of their entry into the organism. Whenever the initial contact of TS is made, either no changes occur, or they are very insignificant. Upon the action of PhOS on the skin, the mucous membranes of the respiratory tracts, and the organs of digestion no affections are observed whatsoever; only upon the action of isolated representatives of this TS group on the skin some weakly

manifested hyperemia and edema are observed. In some animals (horses, cows) the skin affections may be more pronounced, sometimes proceeding to the formation of blisters full of a sero-fibrinous exudate; in cows ulcerations covered with crust are at times observed.

The poisoning originates in an identical form in all the pathways of penetration of TS into the organism; therefore, the affections connected with various forms of PhOS application need not be described separately. The toxic picture develops rapidly and is manifested in forms not uniform in gravity. The mildest of these forms is manifested in symptoms of myosis where the pupil may be reduced in size to that of a pinhead. In more marked poisoning, bronchospasm accompanied by disturbances of respiration attract attention. The graver form of intoxication manifests itself through extensive and pronounced affections of the nervous system -- the cerebrum spinal cord, and various links of the involuntary innervation; there are observed: contraction of the pupils (Fig. 1), cyanosis of the skin of the face, secretion of mucus from the oral cavity and nose, clonic and tonic convulsions of the muscles of the extremities and body, loss of consciousness, and death.

When the toxic effect was considerable and the treatment could not be carried out in time and effectively, death may occur rapidly. About half of the poisoned animals perish within a few minutes to one hour; the majority perish during the acute stage following poisoning (up to three days) and only a few animals survive up to 10 days or longer.

In the entire picture of PhOS-poisoning the affections of the nervous system predominate; therefore these are considered first in discussing the pathological anatomy of a given poisoning.

When death is rapid, a slight hyperemia of the soft cerebral membrane and a moderate edema of this membrane and the cerebral tissue are observed; petechia are observed in the same organs.

Changes in the cerebrum fairly typical for PhOS are observed under microscopic examination. The soft cerebral membrane and the cerebral substance are edematous. Pictures of a pronounced subependymal edema are encountered (Fig. 2). The blood vessels are filled with blood and show fatty degeneration of their epithelium. The hemorrhages present cannot be explained by convulsions which, as mentioned above, accompany poisoning, since a preliminary administration of narcotics or curare to animals does not prevent hemorrhages in the cerebral tissue. They are rarely large; usually they belong to the category of small ones (Fig. 3).

The localization of hemorrhages in the cerebral tissue varies greatly: they are found in the cortex, as well as in the subcortical nodes, brain stem, and cerebellum. The hemorrhages are situated around blood vessels of various sizes (from relatively large ones to arterioles and capillaries), and are caused by permeability of

vascular walls as well as by diapedesis; impairment of the vascular wall permeability even without mechanical damage to the wall may lead to fairly extensive hemorrhages. On the other hand, hemorrhages may be absent even when death has occurred during the acute stage.



Fig. 2.

PhOS. Brain of cat (pons varolii). Pronounced subependymal edema (death within six hours).

Many hemorrhages have a clearly expressed perivascular character. The erythrocytes are found at times in the edematous fluid or they adjoin closely to each other and destroy the cerebral tissue which surrounds the vessel. At times the walls of the vessel form scalloped protrusions of basophile staining; the endothelium is peeled off. If the hemorrhages are very small, the capillaries around which they emerge can not be detected.

The assumption that brain hemorrhages caused by PhOS are related to impairments of the arteriolar function is supported by the fact that, in addition to the non-uniform contractions and dilatations of the arterioles, the fine lacerations of the elastic tissue resemble similar changes induced by prussic acid poisoning (see below).

On the longitudinal sections of small cerebral arterioles an occasional spasmodic contraction of their muscular sheath results in a nonuniform change of the lumen; at times bead-like dilatations of irregular outlines can be seen along the length of the vessels, with a narrowing of the vascular lumen between these dilatations (Fig. 4). The layer of the cerebral tissue which surrounds the vessel is permeated with edematous fluid; an exit protoplasm is observed beyond the limits of the

vessel, of the type known as serous apoplexy (Fig. 5). The edematous fluid pushes apart the glial elements, and surrounds the ganglionic cells; also pericellular edema appears (Fig. 6). Some authors consider the saturation of the soft cerebral membrane with edematous fluid as a serous meningitis; it seems to me, however, that there is not sufficient basis for that.

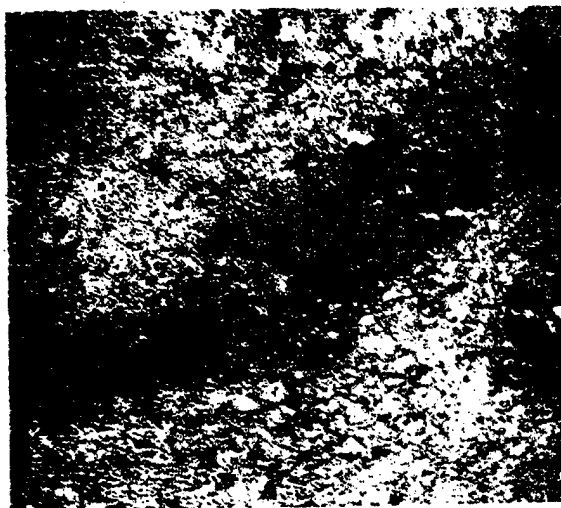


Fig. 3

PhOS. Brain of cat. A -- small hemorrhages (death during the acute stage). B -- cerebral cortex; hemorrhage; necrosis of the ganglion cell (death within two hours).



Fig. 4.

PhOS. Irregular spasmodic contraction of the muscular sheath of a small cerebral artery of a cat; perivascular edema (death during the acute stage).

One could assume that the hemorrhages in the cerebral substance specifically cause the destructive changes in the nervous system. This is not entirely true, however. The cause of these affections lies in the extensive impairment of vascular functions which create disturbances of nutrition and metabolism in the cerebral elements (especially oxygen hunger to which the ganglionic cells are very sensitive). The hemorrhages themselves are caused by spasmodic vascular contractions alternating with irregular dilatations; these functional disturbances lead to small lacerations in the vascular walls and to increased permeability to the plasma and erythrocytes.

The hemorrhages and dystrophic changes of nervous cells result from one factor: impairment of cerebral blood supply. Presumably, the point of application of PhOS action is in the receptors of the vascular walls. It also plays a part in the pathogenesis of affections in other organs of which we shall speak later. The earliest blood circulation disturbances in the brain assume particular importance because ganglionic cells are especially susceptible to vascular disturbances, and the affections of neural elements of the brain are of exceptional significance to the entire organism and its separate organs. One can not of course deny also the direct effect of PhOS on the ganglionic cells, particularly on their synaptic mechanisms.

Death from PhOS poisoning may set in so rapidly that the morphologically elicited affections of the ganglionic cells

of the brain may not have time to develop. Later, dystrophic changes of neural cells begin to emerge in various sections of the brain: the cerebral cortex, stem section, the large gray nodes of the base, horn of Ammon, and cerebellum. The degeneration of ganglionic cells is often particularly clearly seen in the sections of the brain showing considerable vascular disturbances.

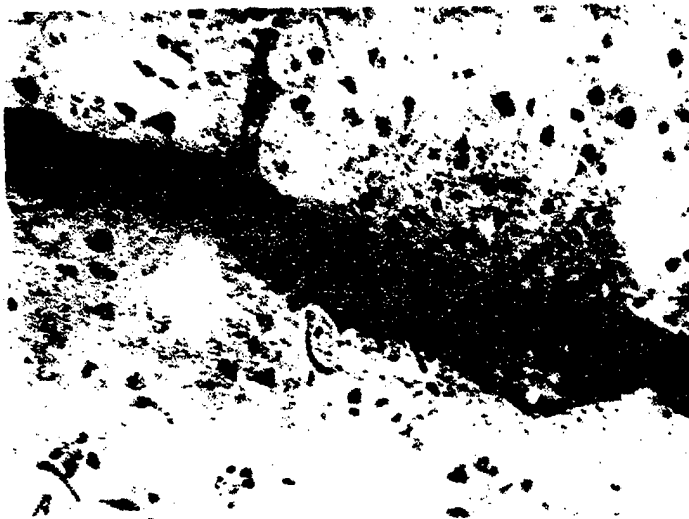


Fig. 5.
PhOS. Cerebral cortex of cat. A -- perivascular hemorrhage and serous apoplexy (death within two hours); B -- serous apoplexy (death within 24 hours).

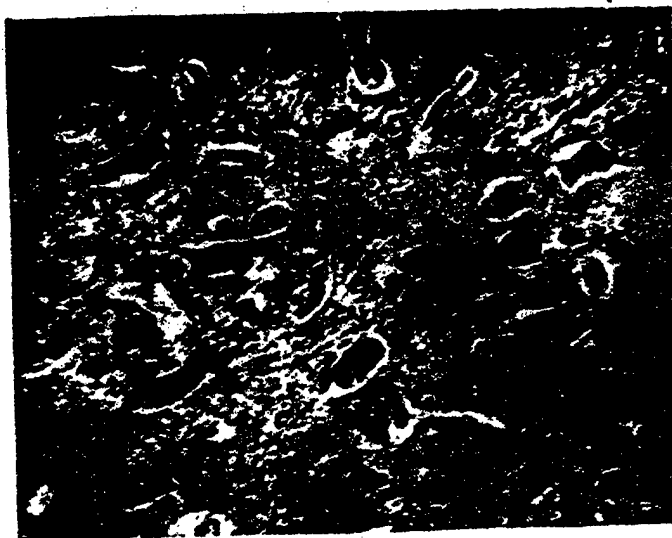


Fig. 6.
PhOS. Cat's brain (gray nodes of the base).
Pronounced pericellular edema (death within
one hour).

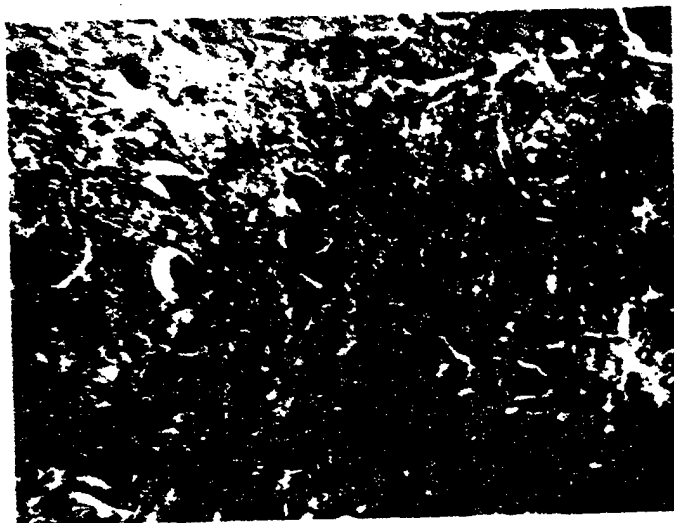


Fig. 7.
PhOS. Cat's brain. Hyperchromic and shriveled
ganglionic cells (death within six hours).

Some of the cerebral neural cells show a hyperchromia of the protoplasm and its basophilia and shriveling of the cellular body (Fig. 7). There is pyknosis of the nuclei the outlines of which become angular. The nucleus is displaced to the periphery

of the cell, the chromatin condenses, and the nucleolus is poorly discernible; in some cells karyopyknosis is substituted by karyorrhexis. Other ganglionic cells reveal paler staining than usual; the Nissl's granules become indistinct; the granules are unevenly distributed and disappear in some cells; vacuoli appear in the protoplasm (Fig. 8). The nuclei of neural cells become distended and poorly stained and disappear completely under conditions of kariolysis. A zone of acidophilia of the protoplasm around the neural cell nuclei, decentralization of the nuclei and their disappearance is described by some authors.



Fig. 8.

PhOS. Cat's brain (gray nodes at the base. Edema of the cerebral tissues; vacuolization of a ganglionic cell; pericellular edema (death within two hours).

Edema of the cerebral substance, at times of a fecal character, may be accompanied by pericellular edema (Fig. 6.). The appearance in the protoplasm of cavities filled with fluid is observed also in some cases not associated with cerebral edema; the vacuoles are at times round, at other times they have irregular outlines; the content of vacuoles gives no reaction to fat.

The neural cell affections are elicited also on silver-impregnated preparations. The intracellular fibrils disappear, the protuberances thicken, and their argyrophilia increases; at later periods, following poisoning, an elongation of protuberances, spiral twisting, and mace-like and ball-like thickenings are observed. Very pronounced dystrophic affections of neural cells may lead to their death.

The above described affections of ganglionic cells have no definite localization: they can be found in various sections of

the brain. Not only the degree but also the number of affected cells may fluctuate widely depending on the gravity of the toxic effect, rapidity of the onset of death, and the different intensity of blood- and lymphocirculation disturbance. The morphological changes of neural cells are particularly pronounced in those cases when death occurs within a few hours (or scores of hours) after poisoning. In cases of a more remote onset of death, the glial cells proliferate and arrange themselves in the form of rosettes around dying ganglionic cells.

In cases where death occurs not immediately after poisoning, an edema of the white cerebral substance can be seen under the microscope; the cortical neural cells are either unchanged, or present a picture of a so-called grave affection (Nissl). Pronounced dystrophic changes of ganglionic cells of the cerebral cortex and Purkinje cells of the cerebellum are observed. The affections of the central nervous system may in themselves cause death at a later stage; besides, the cerebral changes may play the role of reducing the adaptive and compensatory potency of the organism, leading to unfavorable complications which directly cause death; we shall come back to this problem later.

The affections of the spinal cord resemble those of the brain in many respects; plethora of the spinal cord substance and its soft membrane are noted. In the spinal cord, as in the brain tissue, a contraction of the vascular lumen alternates with irregular dilatations. Also in the spinal cord, fine lacerations in the elastic tissue indicate spasmodic contractions of the small arteries. Impairments of the permeability of vascular walls lead to a perivascular edema and focal serous apoplexies.

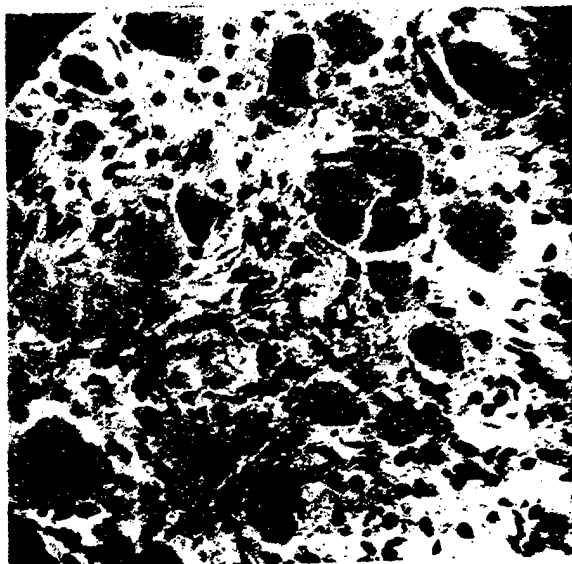


Fig. 9.

PhOS. Cervical sympathetic node of a cat. Degenerative changes of ganglionic cells (death within 42 hours).

The lacerations in the vascular walls and impairments of their permeability lead to perivascular hemorrhages; the latter can be very small or more extensive (sometimes as a result of confluence of small hemorrhages). The localization of hemorrhages is rather variegated. There are indications that they are found in the cervical, more frequently than in the sacral or lumbar section of the spinal cord; hemorrhages originate more easily in the gray matter (especially in the anterior cornua) than in the white matter. Plethora and small hemorrhages are encountered also in the spinal ganglions.



Fig. 10.

PhOS. A -- muscular spasm of a bronchus in a cat, swelling of the epithelium. Atelectasis of the peribronchial tissue (acute death). B -- bronchial spasm, large magnification.

In connection with disturbances of blood supply in the spinal cord and, possible also as a result of the direct TS effect on the neural cells, dystrophic changes are observed in the latter. They are located in the anterior, posterior, and lateral horns and resemble the already described affections of ganglionic cells of the brain. Some neural cells show distention of the protoplasm and nucleus -- at times, vacuolization and disappearance of the granularity of the protoplasm. Other cells become pynotic and shriveled and show increased argentophilia upon impregnation. The protuberances of some cells are irregularly thickened on account of spindle-like bulging along their length and terminate in mace-like thickening.

Disturbances of blood circulation and dystrophic changes are observed in the vegetative neural nodes (Fig. 9.), the parasympathetic ganglions being most affected. Small hemorrhages are encountered in the cervical node of the vagus nerve; the vacuolization of protoplasm in the ganglionic cells sometimes has a foamy appearance; some cells and their protuberances show increased argentophilia.

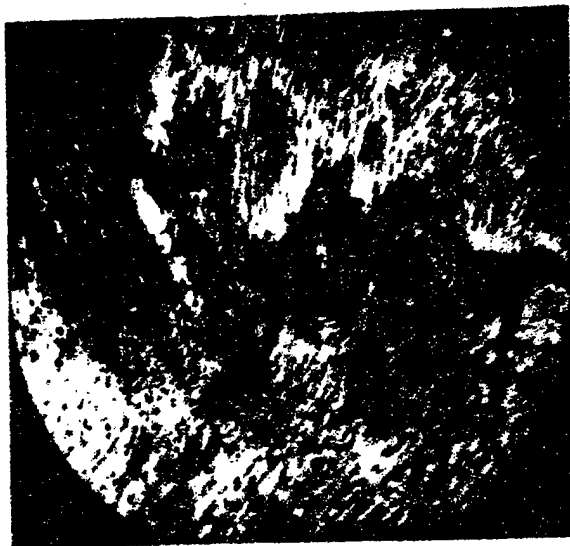


Fig. 11.

PhOS. Heart of a cat. Small foci of hemorrhages and necrosis of myocardium (death within two and one-half hours).

In an acute onset of death the cervical sympathetic nodes and solar plexus reveal plethoric phenomena. Some of the neural cells are marked by pronounced basophilia; the protoplasm as well as nuclei are pyknotic; the cells are shriveled, their outlines are angular; some vacuolized ganglionic cells are encountered.

The above-described dystrophic cellular changes of various sections of the nervous system are found in various combinations, and the toxic effects may be expressed in various degrees in clinically similar cases; one can not speak of a strict correspondence between the gravity of the intoxication and the range of morphological changes in the ganglionic cells.

The affections of the nervous system in those who perish during a much later period have been insufficiently studied. In these cases, parallel with symptoms of prior hemorrhages, fresh hemorrhages appear to result from destruction of blood vessels whose walls show dystrophic changes, particularly swelling and fatty degeneration of the endothelium. Dystrophic phenomena are observed in neural cells in the form of pyknosis, shriveling, argentophilia, and fragmentation of protuberances. Sometimes glia-cell proliferation and pictures of neuronophagy are observed, as well as disintegration of myelin in the axis cylinders of the neural fibers.



Fig. 12.

PhOS. Heart of a cat. Homogenization ("hyaline necrosis") of separate muscular fibers, small hemorrhages (death within 40 minutes).

The affections of the central nervous system which play a principal role in the PhOS toxic picture are caused, as mentioned above, by the impairment of cerebral vascularization. Disturbances of blood circulation and innervation are the outstanding factors in the pathogenesis of affections of the internal organs. In cases of death shortly after poisoning, the organs of respiration and digestion, the heart, and kidneys reveal plethora and hemorrhages followed by dystrophic changes. Disturbances of innervation lead

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to spastic contractions of the smooth muscles manifested in myosis, and spasm of the bronchi and intestines.

If the death of PhOS victims occurs within a short period of time (from several minutes to a few hours), rigor mortis develops rapidly and is markedly pronounced; this is due to the convulsions preceding death.

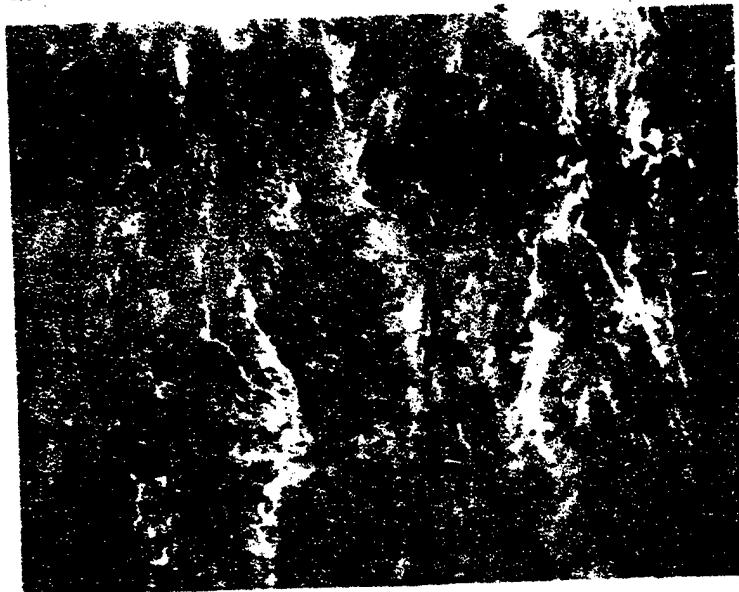


Fig. 13.

PhOS. Heart of a cat. Focus of micromyomatia (death within 24 hours).

In cases where the poisoned individual was subjected to the action of PhOS fumes, one can observe a spastic contraction of the muscles of the pupils in the form of myosis (Fig. 11). This phenomenon takes place also upon contact of relatively large quantities of TS with the skin or with the digestive tract. A direct action of PhOS on one eye may have a stronger effect on it than on the other eye. The spastic muscular contraction of the eye pupils is preserved in the corpse and is important as a differential diagnostic symptom, which facilitates the recognition of PhOS intoxications. The spastic contraction of the intestinal and bronchial musculature is interesting from the same point of view (see below).

Cyanosis of the integumenta may take place when the onset of death is rapid. There is a mucous discharge from the mouth and nose, but the mucous lining of the upper respiratory tract, trachea, and large bronchi remain intact. When death occurs shortly after poisoning (within a few minutes or an hour,) one can see under the microscope signs of spasmodic contractions of the musculature of small bronchi; their lumen is narrowed and the mucous membrane is in the shape of longitudinally situated folds so that on the cross

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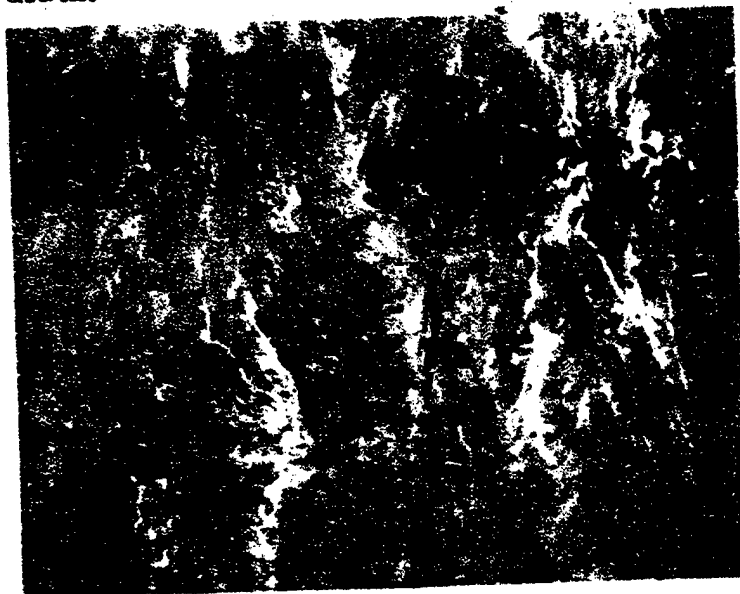


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section of the bronchus it has a scalloped appearance (Fig. 10). Under these conditions an accumulation of even small quantities of mucus in the bronchi may lead to a focal atelectasis of pulmonary tissue.



Fig. 14.

A -- spasm of the musculature of loops of the small intestine of a cat (death within 15 minutes). B -- microphotograph of a preparation from the same cat; the contraction waves of the muscular membrane are seen.

The lungs are plethoric; under the pleura and in the pulmonary tissue are encountered hemorrhages, usually small ones which sometimes become confluent. The pulmonary tissue is airy, in places even somewhat emphysematously inflated. Between the emphysematous areas are found sunken foci of plethoric pulmonary tissue (atelectases). At times a small quantity of foamy fluid runs off the surface of the cut (slight edema).

Under macroscopic examination the cavities of some alveoli show a relatively small quantity of edematous fluid; other alveoli are filled, even distended with air. Small foci of edema, atelectasis, and emphysema alternate and combine between themselves. In some cases within a few days after poisoning a small focal pneumonia may develop.

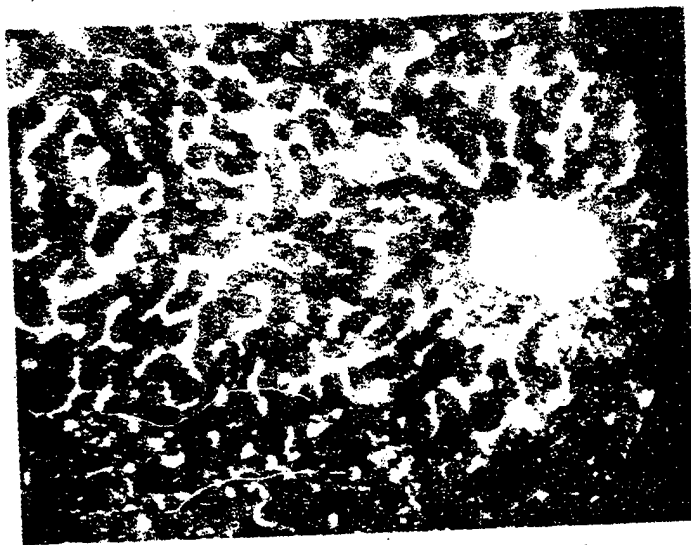


Fig. 15.

PhOS. Liver of a cat. Focus of subcapsular dissociation of liver columns (death within 24 hours).

The cardiac cavities, the right ones in particular, are somewhat dilated and filled with blood with a small quantity of red clots. Petechiae are observed under the endocardium and epicardium. Histological examination reveals small hemorrhages in the myocardium (Fig. 11) and, sometimes, edema. Dystrophic changes of muscular fibers develop rather rapidly; they are manifested in homogenization of the fibers which lose their transverse striated structure, as seen when stained with hematoxylin-eosin but particularly well revealed with ferric hematoxylin. The protoplasm of some muscular fibers undergoes disintegration into protein flocculates of various sizes. The protoplasm of other fibers, on the contrary, appears condensed, homogenized, and

basophilic; the transverse striation disappears and the picture of a so-called "hyaline necrosis" of the fibers is observed (Fig. 12). Parallel with protein dystrophia a dust-like and small-like fatty degeneration of the myocardium is observed. The dystrophic affections of the latter generally have a focal, saic-like character. To determine their volume and topography sections through the entire wall of each of the ventricles (from the bases to the top) and through the entire area of the interventricular septum must be prepared. Not infrequently there are in the myocardium small foci of dystrophy and necrosis of muscular fibers (the so-called micromyomalatae, Fig. 13).

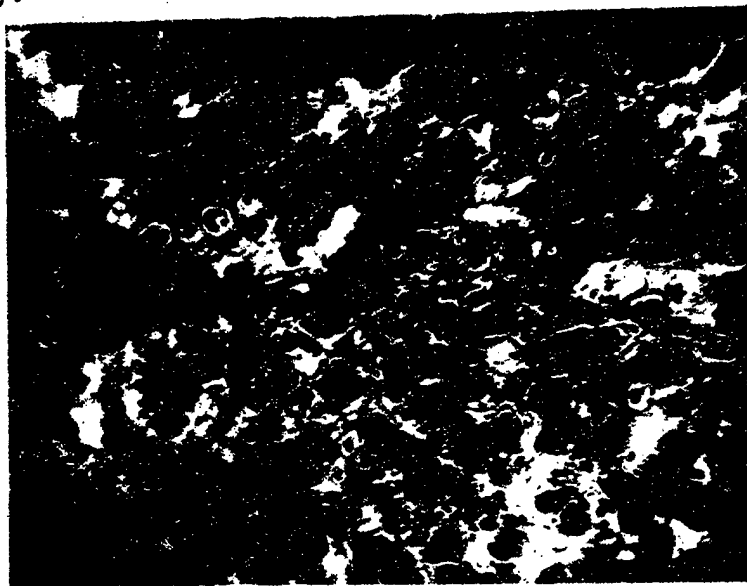


Fig. 16.

PhOS. Liver of a cat. Considerable destructive changes of liver cells ending in their disintegration (death within three hours).

The gastric mucose is plethoric. Small hemorrhages are seen at the tops of folds. Similar changes are encountered in the intestinal mucose. The muscular spasm of the intestinal walls creates an unique picture: along the intestinal loops there are areas of spastic contraction of the musculature of the intestinal wall which becomes bead-like as a result (Fig. 14, A). The spastic contractions of the muscular membrane are observed where death has occurred during the acute stage, and on histological preparations in the form of so-called contraction waves (Fig. 14, B).

The liver tissue is plethoric and petechia are encountered under the capsule. Plethora and small- and large-drop fatty degeneration of liver cells is seen on histological examination. Under the capsule some foci of dissociation of hepatic columns (Fig. 15) are seen as well as the destruction of hepatic tissue; the cells

are intensively stained and appear empty as a result of liquefaction of the protoplasm (they contain no fat or glycogen); on the preparation stained with hematoxylin and eosin the above-described pale areas of destruction and disintegration of liver tissue are clearly visible under small magnification. Also numerous small foci of necrosis of liver tissue are encountered, with the cells broken up into small particles which give no reaction on fat (Fig. 16). The above described changes are, obviously, associated with disturbances of neurogenic origin.

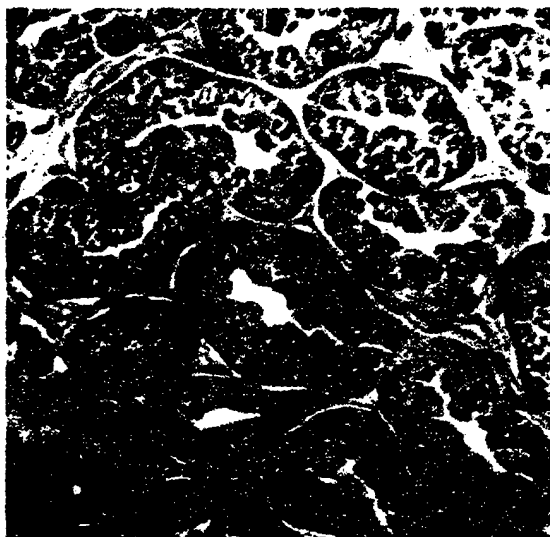


Fig. 17.

PhOS. Granular dystrophy of the epithelium of the winding canaliculi of cat kidney (acute death).

Pronounced multiple hemorrhages which merge into large foci are observed in the pancreas (more frequently in dogs); they are seen under the capsule as well as in the substances of the pancreas. Large hemorrhages of the pancreas may present interest for the differential diagnosis of PhOS poisoning.

The kidney tissue is plethoric; petechia are seen sometimes under the capsule. The epithelium of the winding canaliculi shows a clear picture of protein dystrophy (Fig. 17) and small-drop fatty degeneration.

The spleen plethora varies; at times it is considerable, in other cases it is small; presumably, the muscular spasm of the organ (pronounced in certain experimental animals) contributes to the expulsion of the blood from the net of easily compressed venous vessels of the spleen pulp. If death occurred during the subacute stage, particles of hemosiderin may be deposited in the reticular endothelium of the spleen and liver.

As stated above, a considerable number of PhOS victims perish within the first few minutes or hours; relatively few remain alive for a few days or weeks. Only a small number of animals which die during the acute or more remote stage show no complications, death taking place with progressive anemia and emaciation. As will be shown later (page 35 [of source]), animals subjected to prussic acid poisoning may perish under similar changes. The principal cause of progressive emaciation in such cases is, presumably, the impairments of the cerebral function connected with dystrophic changes in the ganglionic cells. The impairment of cerebral circulation caused by poisoning and, possibly, the direct effect of PhOS on neural cells may induce such drastic disturbances of the function of the central nervous system that death occurs rapidly. But when the poisoned animals do not die immediately, destructive changes develop gradually in the damaged ganglionic cells, leading to very pronounced trophic disturbances. Of course, the cause of trophic impairment cannot be reduced to affections of the cerebral cortex only; we must take into account also the above-described changes in the spinal cord and in the nodes of the involuntary nervous system.

During the remote stage, not infrequently various complications develop, especially of an infectious nature; affections of the nervous system induced by poisoning play an important part in their origin. The infectious process is caused by the interaction of the macro- and micro-organism; the dynamics of development and its outcome depend to a great extent on the nature of the reactivity of the patient. The affections of the nervous system reduce the adaptive and compensatory powers of the organism and place it under favorable conditions if the toxic effects are complicated by infection, not infrequently of an autogenic character. In this case, not only does the infectious process develop more easily, but the fight against it, which essentially involves the task of stimulating the protective and compensatory reactions of the organism, is inhibited.

END

FOR REASONS OF SPEED AND ECONOMY
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